PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/13, 9/107

A1

(11) International Publication Number: WO 99/45946

(43) International Publication Date: 16 September 1999 (16.09.99)

(21) International Application Number: PCT/CA99/00192

(22) International Filing Date: 5 March 1999 (05.03.99)

(30) Priority Data:
329929 9 March 1998 (09.03.98) NZ

(71)(72) Applicant and Inventor: SHERMAN, Bernard, Charles [CA/CA]; 50 Old Colony Road, Willowdale, Ontario M2L 2K1 (CA).

(81) Designated States: CA, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: EMULSION PRECONCENTRATES COMPRISING A CYCLOSPORIN AND GLYCERIDES

(57) Abstract

Pharmaceutical compositions in the form of an ethanol-free emulsion preconcentrates which comprises a cyclosporin as active ingredient, a lipophilic solvent selected from glycerides, a hydrophilic solvent selected from propylene glycol and polyethylene glycol, a surfactant selected from polyoxyethylene glycolated natural or hydrogenated vegetable oil, and a co-surfactant preferably selected from polyoxyethylene-sorbitan-fatty acid esters.

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EMULSION PRECONCENTRATES COMPRISING A CYCLOSPORIN AND GLYCERIDES

TECHNICAL FIELD

The invention is directed to pharmaceutical compositions which facilitate the administration of cyclosporins.

BACKGROUND ART

The term "solvent system" as used herein refers to a carrier in which an active drug (i.e. a cyclosporin) is dissolved. The solvent system may be a single solvent or a mixture of ingredients included as solvents, surfactants, diluents, or for other purposes.

The term "cyclosporin" as used herein refers to any member of a class of nonpolar polypeptides, as defined in the Merck Index, Twelfth Edition. One suchcyclosporin is cyclosporin A, also known as "cyclosporine" and hereinafter referred to as "cyclosporine", known to be therapeutically active as an immunosuppressant.

Cyclosporins are hydrophobic and have low solubility in aqueous media. This makes it difficult to design pharmaceutical compositions (i.e. dosage forms) comprising cyclosporins which exhibit satisfactory absorption into systemic circulation after oral administration, or absorption into the target tissue upon topical administration.

The cyclosporin can be dissolved in an organic solvent (e.g. ethanol or propylene glycol), but if the solvent is water-miscible, when the composition is mixed with gastrointestinal fluid or other aqueous medium, the cyclosporin will precipitate.

Methods of overcoming this problem are known in the prior art. The most common approach is to dissolve the cyclosporin in a solvent system that comprises at least one lipophilic (hydrophobic) solvent and a surfactant, so that the composition disperses into an emulsion when mixed into gastrointestinal fluid or other aqueous medium.

Such compositions are called " mulsion preconcentrates".

U.S. patent 4388307 discloses such compositions. A commercial product that has been sold under the trademark "Sandimmune" is made according to U.S. patent 4388307, and, more specifically, comprises cyclosporine dissolved in a solvent system comprising ethanol as hydrophilic solvent, a vegetable oil as lipophilic solvent, and a surfactant. The ethanol is required to dissolve the cyclosporine in the compositions as the vegetable oil has inadequate capacity to dissolve cyclosporins. While this composition is superior to previously known compositions, it still exhibits absorption that is less than the maximum possible and is variable. Moreover, the use of ethanol has disadvantages, as ethanol is volatile, and Sandimmune capsules must be individually packaged in metallic pouches to avoid evaporation of the ethanol.

U.S. patent 5342625 discloses compositions that are superior in certain respects to the compositions taught in U.S. patent 4388307. The compositions of U.S. patent 5342625 comprise (in addition to the cyclosporin, a lipophilic solvent and surfactant) a hydrophilic solvent which is of either propylene glycol or an alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol.

It is also disclosed that compositions according to U.S. patent 5342625, when added to water, disperse into emulsions with droplet size of less than 2000 , which is smaller than obtained with prior art compositions, thus leading to improved absorption.

Emulsions with droplet size of less than 2000 are defined as "microemulsions". Compositions that, upon addition to water, disperse into microemulsions are called "microemulsion preconcentrates".

Canadian Patent 2072509 discloses microemulsion preconcentrates comprising a cyclosporin dissolved in a carrier which comprises:

(i) as hydrophilic solvent propylene glycol, either alone or with other lower alkanols e.g. ethanol;

(ii) as lipophilic solvent a mixed mono-, di- and tri-glyceride; and

(iii) a surfactant.

The compositions taught by Canadian Patent 2072509 appear to be within the scope of Claim 1 of US Patent 5342625, but limited to propylene glycol as hydrophilic solvent and a mixed mono-, di- and tri-glyceride as lipophilic solvent.

A composition made according to the disclosure of Canadian patent 2072509 is now marketed under the trademark "Neoral", in the form of both an oral liquid which is a microemulsion preconcentrate intended to be diluted into an aqueous drink before ingestion, and a soft gelatin capsule containing the microemulsion preconcentrate.

For both the soft gelatin capsules and the oral liquid, the labelling indicates that the "Neoral" emulsion preconcentrate comprises cyclosporine dissolved in ethanol and propylene glycol as hydrophilic solvents, corn oil glycerides as lipophilic solvent, and polyoxyl 40 hydrogenated castor oil as surfactant. It also contains dl-alpha-tocopherol at a level of about one percent by weight as antioxidant. Although Canadian patent 2072509 includes some examples without ethanol, the use of ethanol inthe commercial "Neoral" product indicates that compositions without ethanol either were not found to give adequate stability or were not found to give adequate absorption upon ingestion.

While Neoral does enable improved absorpti n relative to Sandimmune, it still has certain undesirable properties. Specifically, ethanol is volatile, so that the compositions have to be specially packaged to prevent evaporation of the ethanol.

Several prior art publications disclose further improvements achieved by selecting different lipophilic and/or hydrophilic solvents.

International Publication Number W094/25068 discloses improved compositions in the form of microemulsion preconcentrates in which the principal solvent for the cyclosporin is an alcohol which is selected from alcohols having a boiling point above 100 C and a solubility in water of under 10 g per 100 g at 20 C. Because such alcohols are good solvents for cyclosporine, they eliminate the need for ethanol. Preferred alcohols, within the scope of the disclosure of W094/25068, are saturated alkyl alcohols having 8 to 14 carbon atoms per molecule, including 1-octyl, 2-octyl, 1-decyl, 1-dodecyl and 1-tetradecyl alcohols. However, a problem with such compositions is that they are more toxic than other lipophilic solvents generally used in the art.

New Zealand Patent Application No. 280689 discloses improved microemulsion preconcentrates in which a cyclosporin is dissolved in a solvent system comprising a lipophilic solvent, a hydrophilic solvent and a surfactant, wherein the lipophilic solvent is selected from tocol, tocopherols and tocotrienols, and derivatives thereof, including specifically Vitamin E.

New Zealand Patent Application No. 280689 further discloses use of propylene carbonate as hydrophilic solvent.

Preferred compositions within the scope of New Zealand Patent application No. 280689 comprise both a lipophilic solvent selected from tocol, tocopherols and tocotrienols and derivatives thereof, including specifically Vitamin E. While these compositions exhibit improved properties over the prior art, the disclosed lipophilic solvent such as Vitamin E are relatively expensive.

New Zealand Patent Application No. 314701 provides a pharmaceutical composition in the form of a microemulsion preconcentrate comprising a cyclosporin dissolved in a solvent system comprising propylene carbonate as hydrophilic solvent, a lipophilic solvent selected from glycerides, and at least one surfactant. Such compositions overcome some problem of the prior art. However, propylene carbonate is not an ingredient presently approved by the United States Food and Drug Administration ("FDA") for oral ingestion.

Accordingly, it is the object of the present invention to enable a microemulsion preconcentrate comprising a cyclosporin, which has all the following properties:

1. It contains, as inactive ingredients, only ingredients approved by the FDA for pharmaceuticals for oral administration.

2. It does not contain ethanol or any other volatile solvent.
3. It is stable against precipitation of the cyclosporin.

SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical composition in the form of an emulsion preconcentrate or microemulsion preconcentrate comprising a cyclosporin dissolved in a solvent system which is free of ethanol and comprises:

1. A lipophilic solvent selected from glycerides.

2. Propylene glycol or polyethylene glycol as hydrophilic solvent.

3. Polyoxyethylene glycolated natural or hydrogenated vegetable oil, as surfactant, and

4. A co-surfactant selected from polyoxyethylene-sorbitan-fatty acid esters.

The composition will optimally and preferably also comprise benzyl alcohol as hydrophilic co-solvent.

DETAILED DESCRIPTION OF THE INVENTION

As aforesaid, compositions within the scope of the present invention will comprise a lipophilic solvent selected from glycerides. For purposes of the within specification and claims, the term "glycerides" is to be understood to include mono-, di-, and tri-esters of glycerol with fatty acids, and mixtures thereof.

"Fatty acids" will be understood to include both medium chain (e.g. C_8 - C_{10}) fatty acids and long chain (e.g. C_{12} - C_{18}) fatty acids, both unsaturated and saturated.

It will be understood that an unreacted glycerol molecule has three hydroxyl moieties. Monoglyceride will have two unreacted hydroxyls, diglycerides will have one, and triglycerides will have none.

Hence, mono- and di-glycerides formed by glycerol and fatty acids are capable of further esterification at the remaining one or two hydroxyls.

For the purposes of the within specification and claims, the term 'glycerides" is to be understood to include compounds formed by further esterification of fatty acid mono- and di-glycerides with acids other than fatty acids.

This will include, for xample, acetylated monoglycerid s which are formed by reacting fats with glycerol and triacetin.

Glycerides useable within the scope of the invention will thus include, but not be limited to, the following:

i) vegetable oils (which are comprised primarily of fatty acid triglycerides), and extracts therefrom.

ii) any of the mono- or diglycerides approved for pharmaceutical use, including, for example, glyceryl mono-oleate.

iii) a mixed mono-, di-, and triglyceride, which will preferably comprise a mixture of C_{12-20} fatty acid mono-, di- and triglycerides.

Preferably these mixed glycerides are predominantly comprised of unsaturated fatty acid residues, in particular C_{18} unsaturated fatty acid residues such as linolenic, linoleic and oleic acid residues.

The mixed mono-, di-, and tri-glycerides are preferably predominantly comprised of mono- and di-glycerides.

The mixed mono-, di-, and tri-glycerides may be prepared by admixing individual mono-, di, and tri-glycerides in appropriate relative proportions. Conveniently, however, the mixed glycerides comprise transesterification products of vegetable oils, for example almond oil, ground nut oil, olive oil, peach oil, palm oil, soybean oil, corn oil, sunflower oil or safflower oil, with glycerol. Preferably the vegetable oil is corn oil. Also, mixtures of the oils may be transesterified with glycerol.

The transesterification products are generally obtained by heating the selected vegetable oil with glycerol to effect transesterification or glycerolysis. This may be carried out at high temperature in the presence of an appropriate catalyst, under an inert atmosphere and with continuous agitation. In addition to the mono-, di- and tri-glyceride components, the transesterification products also generally comprise minor amounts of free glycerol.

Transesterification products of corn oil and glycerol provide particularly suitable mixed mono-, di-, and tri-glycerides. An example of a suitable mixed glyceride product is the transesterification product commercially available under the trade name MAISINE (available from the company Etablissements Gattefosse, of 36 Chemin de Genas, P.O. Box 603, 69804 Saint-Priest, Cedex (France)). This product is comprised predominantly of linoleic and oleic acid mono-, di- and tri-glycerides together with minor amounts of palmitic and stearic acid mono-, di- and tri-glycerides.

iv) Acetylated monoglycerides which consist of glycerol esterified with fatty acids at one of the three hydroxyl functions, with the other two hydroxyls replaced by an acetyl moieties.

Acetylated monoglycerides are sold in the United States under the tradename "Myvacet" by Eastman Chemical Products Inc. They are made by reacting fats with glycerine and triacetin.

By adjusting the degree of saturation of the monoglyceride and the degree of acetylation, different characteristics are obtained.

Fully acetylated monoglycerides prepared from unsaturated mono-glycerides are liquids at room temperature. In this context, the phrase □fully acetylated□ is intended to mean having a minimum acetylation of about 96%.

Fully acetylated monoglycerides are currently available from Eastman Chemical Products Inc. under the designations Myvacet 9-08 and Myvacet 9-45. For Myvacet 9-08, the fat source is hydrogenated coconut oil. For Myvacet 9-45 the fat source is partially hydrogenated soybean oil.

Myvacet 9-08 and Myvacet 9-45 are both liquids at room temperature, having melting points of 4 C to 12 C. Both are well suited for use as lipophilic solvent, but Myvacet 9-45 is especially preferred because of its lower cost.

The preferred glycerides are mixed mono-, di- and tri-glycerides and acetylated monoglycerides because of the advantages of low cost and being good solvents for cyclosporins.

As aforesaid, compositions with the scope of the present invention will further comprise as hydrophilic solvent, either propylene glycol or polyethylene glycol. When polyethylene glycol is used, it will preferably have a mean molecular weight of less than 1000. More preferably the mean molecular weight will be from about 400 to about 200, even more preferably from about 300 to about 200, and most preferably it will be about 200.

As aforesaid, the composition will optimally and preferably also contain benzyl alcohol as hydrophilic co-solvent.

As aforesaid, compositions within the scope of the present invention will further comprise, as surfactant, a polyoxyethylene glycolated natural or hydrogenated vegetable oil; for example, polyoxyethylene glycolated natural or hydrogenated castor oil. Particularly preferred is the surfactant designated in the United States Pharmacopoeia and National Formulary as Polyoxyl 40 Hydrogenated Castor Oil, which is available under the tradename "Cremophor RH40".

The stability of the composition and the dispersibility in water can be improv d by including in the composition a co-surfactant. Preferred co-surfactants are selected from polyoxyethylene-sorbitan-fatty acid esters; e.g. mono- and trilauryl, palmityl, stearyl and oleyl esters; e.g. products of the type known as polysorbates and available under the tradename "Tween". Especially preferred as co-surfactant are polyoxyethylene (20) sorbitan monolaurate, which is also known as polysorbate 20, and polyoxyethylene (20) sorbitan monooleate, which is also known as polysorbate 80.

Compositions in accordance with the present invention may also contain other ingredients.

For example, the composition may include, in addition to the foregoing, one or more other ingredients that are included as diluents, thickening agents, anti-oxidants, flavouring agents, and so forth.

Compositions in accordance with the invention may comprise dosage forms for direct administration as emulsion preconcentrates or microemulsion preconcentrates. For example, an emulsion preconcentrate or microemulsion preconcentrate may be directly used as liquid for oral ingestion, parenteral use, or topical application, or it may be encapsulated into gelatin capsules for oral ingestion.

However, the present invention also provides pharmaceutical compositions in which the emulsion preconcentrate or microemulsion preconcentrate is further processed into an emulsion or a microemulsion. Thus, where oral administration is practised, emulsions or microemulsions obtained, e.g. by diluting a preconcentrate with water or other aqueous medium (for example, a sweetened or flavoured preparation for drinking), may be employed as formulations for drinking. Similarly, where topical application is intended, compositions comprising an emulsion preconcentrate, a thickening agent, and water will provide an aqueous emulsion in gel, paste, cream or like form.

Compositions in accordance with the present invention, whether emulsion preconcentrates, microemulsion preconcentrates, emulsions, or micr emulsions, may be employed for administration in any appropriate manner and form; e.g. orally, parenterally, topically; or rectally.

The relative proportion of the cyclosporin and other ingredients in the compositions of the invention will, of course, vary considerably depending on the particular type of composition concerned; e.g. whether it is an emulsion preconcentrate, microemulsion preconcentrate, emulsion, or microemulsion, the route of administration, and so forth. The relative proportions will also vary depending on the particular ingredients employed and the desired physical characteristics of the composition; e.g. in the case of a composition for topical
use, whether this is to be a free flowing liquid or a paste. Determination of workable proportions in any particular instance will generally be within the capability of persons skilled in the art.

The invention will be more fully understood from the following examples, which are illustrative but not limiting of compositions in accordance with the present invention.

EXAMPLES

In each of the following examples, the ingredients were weighed into a test tube in the proportions shown, the test tubes and contents were warmed to 100 C in a water bath, and then the test tubes were shaken until the contents of each tube wereinterdissolved to form a clear solution.

Then 1 g from the resulting emulsion preconcentrate in each test tube was transferred to another test tube, about 20 ml of warm (37 C) water was added, and the test tube was shaken to disperse the 1 g of the composition in the water to form an emulsion or microemulsion. The resultant emulsions or microemulsions were then compared for clarity by measuring the light transmittance through a 1 cm cell at 600 nm. A higher transmittance indicates a smaller droplet size and hence, a finer emulsion or microemulsion.

Example No.:		1	2	3
Cyclosporine		1.0	1.0	1.0
Maisine	2.1	2.1	2.3	
Propylene Glycol	2.9	2.6	0	
Polyethylene Glycol 200	0	0	2.4	
Benzyl Alcohol		0	0.3	0.4
Cremophor RH40	3.6	3.6	3.5	
Polysorbate 80		1.0	1.0	1.0
Total:		10.6	10.6	10.6
Percent Transmittance at 600 nm		82.8	87.1	80.2

Example No.		4	5	6
Cyclosporine		1.0	1.0	1.0
Myvacet 9-45		1.8	2.4	2.4
Propylene Glycol	3.0	2.3	0	
Polyethylene Glycol 200	0	0	2.3	
Benzyl Alcohol		0.4	0.4	0.4
Cremophor RH40	3.5	3.6	3.5	
Polysorbate 80		1.0	1.0	1.0
Total:		10.7	10.7	10.6
Percent Transmittance at 600 nm		90.0	87.1	84.9

As aforesaid, the transmittance is that of an emulsion or microemulsion made by dispersing 1 g of the composition in about 20 ml of warm (37 C) water.

In each case, the density of the preconcentrate was about 1.06 to 1.07 g/ml, so that each ml of the preconcentrate contained about 100 mg of cyclosporine.

As a basis for comparison, 1 g of the marketed product, Neoral Oral Solution, was similarly dispersed in about 20 ml of warm (37 C) water and the transmittance through 1 cm cell at 600 nm was measured to be 83.9%. The compositions of all of examples 1 to 8 thus all gave transmittance comparable to that of Neoral, which indicates that the microemulsions are as fine as obtained with Neoral.

WHAT I/WE CLAIMED IS:

1. A pharmaceutical composition in the form of an emulsion preconcentrate comprising a cyclosporin dissolved in an ethanol-free solvent system comprising a lipophilic solvent selected from glycerides, a hydrophilic solvent selected from propylene glycol or polyethylene glycol, a surfactant selected from polyoxyethylene glycolated natural or hydrogenated vegetable oils, and a co-surfactant.

2. A composition as in claim 1 wherein the co-surfactant is selected from polyoxyethylene-sorbitan-fatty acid esters.

3. A composition as in claim 1 or 2 that is a micro-emulsion preconcentrate.

4. A composition as in any of claims 1 to 3 wherein the lipophilic solvent is mixed mono-, di-, and tri-glyceride and the hydrophilic solvent is propylene glycol.

5. A composition as in any of claims 1 to 3 wherein the lipophilic solvent is acetylated monoglyceride and the hydrophilic solvent is propylene glycol.

6. A composition as in any of claims 1 to 3 wherein the lipophilic solvent is mixed mono-, di-, and tri-glyceride and the hydrophilic solvent is polyethylene glycol.

7. A composition as in any of claims 1 to 3 wherein the lipophilic solvent is acetylated monoglyceride and the hydrophilic solvent is polyethylene glycol.

8. A composition as in claims 6 or 7 wherein the polyethylene glycol has a mean molecular weight of less than 1000.

9. A composition as in claims 6 or 7 where the polyethyl ne glycol has a mean molecular weight of from about 400 to about 200.

10. A composition as in claims 6 or 7 wherein the polyethylene glycol has a mean molecular weight of from about 300 to about 200.

11. A composition as in claims 6 or 7 wherein the polyethylene glycol has a mean molecular weight of about 200.

12. A composition as in any of claims 1 to11 which also comprises benzyl alcohol.

13. A composition as in any of claims 1 to 12 wherein the surfactant ispolyoxyl 40 hydrogenated castor oil.

14. A composition as in any of claims 1 to 13 wherein the co-surfactant is polysorbate 20 or polysorbate 80.

INTERNATIONAL SEARCH REPORT

Internatic \pplication No
PCT/CA 99/00192

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/13 A61K9/107

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	EP 0 760 237 A (CIPLA LIMITED) 5 March 1997 see page 2, line 39-46 see examples 5,7,9 see claims 2,5,9	1,3,4,14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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